



Case Western Reserve University School of Law Scholarly Commons

Faculty Publications

2003

Regulating Clinical Research: Informed Consent, Privacy, and IRBs

Sharona Hoffman

Case Western Reserve University School of Law, sharona.hoffman@case.edu

Follow this and additional works at: https://scholarlycommons.law.case.edu/faculty_publications

 Part of the [Health Law and Policy Commons](#)

Repository Citation

Hoffman, Sharona, "Regulating Clinical Research: Informed Consent, Privacy, and IRBs" (2003). *Faculty Publications*. 217.

https://scholarlycommons.law.case.edu/faculty_publications/217

This Article is brought to you for free and open access by Case Western Reserve University School of Law Scholarly Commons. It has been accepted for inclusion in Faculty Publications by an authorized administrator of Case Western Reserve University School of Law Scholarly Commons.

REGULATING CLINICAL RESEARCH: INFORMED CONSENT, PRIVACY, AND IRBS

SHARONA HOFFMAN

I. INTRODUCTION

During the past two decades, the United States has experienced dramatic developments in the area of biomedical research.¹ Expanding budgets,² augmented computer capabilities, and the Human Genome Project³ have all significantly enhanced research capabilities.⁴ Consequently, the number of research projects conducted in this country is ever growing,⁵ and the enrollment of an adequate number of human subjects is becoming an increasingly challenging task.⁶ In the words of one commentator, "never have so many human clinical trials been underway and offered so much promise for improving human health . . . [and] never have the economic and regulatory challenges been as great."⁷

Copyright © 2002, Sharona Hoffman

¹ See Beverly Woodward, *Challenges to Human Subject Protections in US Medical Research*, 282 JAMA 1947, 1948 (1999).

² See Harold Y. Vanderpool, *Introduction and Overview: Ethics, Historical Case Studies, and the Research Enterprise*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY* 1, 13 (Harold Y. Vanderpool ed., 1996) [hereinafter *THE ETHICS OF RESEARCH*] ("[F]unding for biomedical research from federal, state, local, philanthropic, and industry sources had reached the amazing sum of \$22.5 billion by 1990."); See also Gregg Easterbrook, *What Went Right: Modest Gain*, *THE NEW REPUBLIC*, Jan. 22, 2001, at 12, 15 (explaining that the National Institutes of Health's (NIH) budget increased 111% during the Clinton presidency).

³ See Leroy Hood & Lee Rowen, *Genes, Genomes and Society*, in *GENETIC SECRETS: PROTECTING PRIVACY AND CONFIDENTIALITY IN THE GENETIC ERA* 3 (Mark A. Rothstein ed., 1997).

⁴ See Woodward, *supra* note 1, at 1948.

⁵ Elizabeth Austin, *Flying Double-Blind Would You Be Willing to Risk Your Health for Science?* CHI. TRIB., Sept. 10, 2000, at 16, 18 ("An estimated 60,000 to 70,000 [clinical] trials are being conducted at any given time in the United States.").

⁶ *Id.* See also, Kurt Eichenwald and Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at 1. The article attributes the proliferation of drug trials in the 1990s to managed care and the restrictions it placed on drug prices. *Id.* Since drug companies were limited in the prices they could charge for each drug, they opted to increase the number of drugs they sold in order to maintain profitability. *Id.* Thus began the industry's "rush to drug development." *Id.*

⁷ Michael J. Malinowski, *Institutional Conflicts and Responsibilities in an Age of Academic-Industry Alliances*, 8 WIDENER L. SYMP. J. 47, 47 (2001) (citation omitted).

Clinical research involving human participants is governed by federal regulations that have been promulgated by the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA).⁸ In light of the proliferation of medical research, however, an increasing number of critics are voicing serious concerns about inadequate enforcement of the regulations and unacceptable research risks.⁹ In recent years, several subjects have died as a result of treatment received in clinical trials and several well-publicized lawsuits have been filed against researchers, research institutions, and institutional review boards (IRBs).¹⁰ The most prominent case is that of Jesse Gelsinger, an eighteen-year old man with a rare metabolic disease, who died while undergoing experimental genetic therapy administered in a clinical study at the University of Pennsylvania.¹¹ In addition, a healthy research volunteer died as a result of an experiment relating to asthma that was conducted at Johns Hopkins School of Medicine.¹² Two recent lawsuits involve individuals who received an experimental melanoma vaccine in a clinical trial conducted at the University of Oklahoma Health Science Center in Tulsa¹³ and patients who participated in blood cancer trials at the Fred

⁸ 21 C.F.R. §§ 50.1-56.124 (2002); 45 C.F.R. §§ 46.101-46.409 (2001).

⁹ See *Protecting Human Clinical Research Patients: Hearing on Institutional Review Boards (IRBS) Before the House Comm. on Gov't Reform & Oversight Subcomm. on Human Resources*, 105th Cong. (1998) (statement of George Grob, Deputy Inspector General for Evaluation and Inspections, Department of Health and Human Resources), available at 1998 WL 12761511 (hereinafter 1998 Hearing).

¹⁰ IRBs are committees designated by research institutions to review, approve, and periodically monitor biomedical research studies. 21 C.F.R. § 56.102(g) (2002); See also 45 C.F.R. § 46.102(g) (2001).

¹¹ Rick Weiss & Deborah Nelson, *Teen Dies Undergoing Experimental Gene Therapy*, WASH. POST, Sept. 29, 1999, at A1; *Gelsinger v. Trustees of the Univ. of Pennsylvania*, No. 000901885 (Philadelphia County Ct. Com. Pl.) (filed Sept. 18, 2000). The lawsuit was settled on Nov. 3, 2000 and the details of the agreement were not released. See Alison Schneider, *U. of Pennsylvania Settles Lawsuit Over Gene-Therapy Death*, CHRON. HIGHER EDUC., Nov. 6, 2000, available at <http://chronicle.com/daily/2001/11/2000/0602n.htm>.

¹² Robert Steinbrook, *Protecting Research Subjects – The Crisis at Johns Hopkins*, 346 N. ENGL. J. MED. 716-720 (2002). In the study, subjects were instructed to inhale a drug called hexamethonium that causes airways to constrict, and physicians observed the subject's airways as they took deep breaths. *Id.* at 717.

¹³ *Robertson v. McGee*, No. 4:01-CV-60 (N.D. Okla.) (filed Jan. 29, 2001). The plaintiffs seek damages arising from alleged failures to comply with the federal regulations that govern biomedical research. *Id.*

Hutchinson Cancer Research Center in Seattle.¹⁴ Intensifying concerns about both human subject welfare and potential liability are stimulating urgent calls for regulatory reforms.

Part I of this Article provides a brief historical overview of Twentieth Century research abuses and the development of regulatory oversight in the United States. Part II discusses informed consent, IRBs, and the regulations that govern them. Part III analyzes contemporary deficiencies in the regulatory system. Finally, Part IV offers recommendations for reform.

II. A HISTORICAL OVERVIEW OF RESEARCH ABUSES AND THE DEVELOPMENT OF RESEARCH REGULATIONS

During World War II, the Nazis conducted large-scale, experiments on concentration camp prisoners that were designed not only to gather medical data, but also to torture and kill the subjects. In some camps, German doctors infected numerous healthy inmates with yellow fever, smallpox, typhus, cholera, and diphtheria germs that caused hundreds of them to die.¹⁵ In other camps Nazi physicians conducted experiments relating to high altitude, malaria, freezing, mustard gas, bone transplantation, sea water, sterilization, and incendiary bombs.¹⁶ The full scope and ghastliness of the Nazi medical experimentation was revealed and documented during the Nuremberg Trials after World War II.¹⁷

In the United States, medical research was conducted for many decades without any regulatory oversight.¹⁸ Perhaps not surprisingly, in an environment devoid of regulation and monitoring, an alarming number of

¹⁴ Wright v. Fred Hutchinson Cancer Research Ctr, No. 01-2-008376 (Kitsap County Sup. Ct. filed Mar. 29, 2001). The complaint alleges that subjects were not fully informed of the study's risks, and that the investigators were unduly influenced by the allure of potential financial profits. *Id.* Eighty of the eighty-two individuals who participated in the trial between 1981 and 1993 died. *Id.*; Vida Foubister, *Lawsuits have doctors wary, but not quitting research yet*, 44 AM. MED. NEWS, Apr. 16, 2001, at 1-2.

¹⁵ ALLEN M. HORNBLUM, *ACRES OF SKIN: HUMAN EXPERIMENTS AT HOLMSBURG PRISON* 75 (1998).

¹⁶ *Id.* at 75-77.

¹⁷ The Nuremberg Trials commenced on November 20, 1945 at the Palace of Justice in Nuremberg, Germany. Fifteen of the twenty-three defendants were found guilty of "war crimes and crimes against humanity," and seven of them were sentenced to death. See Alexander Mitscherlich & Fred Mielke, *Epilogue: Seven Were Hanged*, in THE NAZI DOCTORS AND THE NUREMBERG CODE 105-06; Bernard Meltzer, "War Crimes": *The Nuremberg Trial and the Tribunal for the Former Yugoslavia*, 30 VAL. L. REV. 895, 896 (1996).

¹⁸ Vanderpool, *supra* note 2, at 8.

research abuses occurred in this country as well.¹⁹ In the early 1950s, nearly one hundred percent of participants in Phase I clinical trials, the first and riskiest phase of human research studies,²⁰ were prisoners.²¹ In Ohio, for example, live cancer cells were introduced into both forearms of many prisoners.²² Two weeks after the injection, the affected area of one arm would be surgically removed for study, while the malignant cells were left in the other forearm for further observation.²³ At the Ionia State Hospital in Michigan, at least 142 inmates were recruited for secret CIA psychological experiments.²⁴ As late as 1969, eighty-five percent of new medications were still tested on prisoners.²⁵

Research abuses in the decades following WWII were not limited to the prison environment but also involved other vulnerable populations.²⁶ For example, patients at the Jewish Chronic Disease Hospital in Brooklyn had live cancer cells injected under their skin, and retarded children in the Willowbrook State School on Staten Island were infected with a mild strain of hepatitis.²⁷ The experiments were done without the subjects' knowledge or consent.²⁸

In 1972, news of the notorious Tuskegee syphilis study highlighted the problem of mistreatment of medical research subjects in the United States.²⁹ The Tuskegee study, whose participants were all African-American men, was conducted from 1932 until the beginning of the 1970s and sought to analyze the natural progression of untreated syphilis.³⁰ The researchers, therefore, did not provide patients with penicillin, an antibiotic that is a fully effective cure for syphilis and was widely available as early

¹⁹ *Id.*

²⁰ See 21 C.F.R. § 312.21(a) (2002). Human research studies are often called "clinical trials." *Id.*

²¹ HORNBLUM, *supra* note 15, at 43.

²² HORNBLUM, *supra* note 15, at 93.

²³ HORNBLUM, *supra* note 15, at 93.

²⁴ HORNBLUM, *supra* note 15, at 95.

²⁵ Kathleen Schroeder, *A Recommendation to the FDA Concerning Drug Research on Prisoner*, 56 S. CAL. L. REV. 969, 971 (1983).

²⁶ Henry K. Beecher, *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354, 1354-60 (1966).

²⁷ *Id.* at 1358; Vanderpool, *supra* note 2, at 9.

²⁸ Vanderpool, *supra* note 2, at 9.

²⁹ See Colleen M. McCarthy, Note, *Experimentation on Prisoners: The Inadequacy of Voluntary Consent*, 15 NEW ENG. J. ON CRIM. & CIV. CONFINEMENT 55, 58 (1989); See also Vanderpool, *supra* note 2, at 9. The first report of the study appeared in a July 1972 article by Jean Heller entitled *Syphilis Victims in U.S. Study Went Untreated for 40 Years*.

³⁰ WILLIAM J. CURRAN ET AL., HEALTH CARE LAW AND ETHICS 276 (5th ed. 1998).

as 1953.³¹ The subjects, who believed they were receiving adequate care, continued to suffer unnecessarily from the debilitating effects of the disease.³²

The federal government finally responded to publicity concerning research abuses by promulgating oversight regulations. The FDA and the National Institutes of Health (NIH) developed internal policy guidelines in 1966 and 1971, respectively, and these became federal regulations in 1974.³³ The National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research was established through the National Research Act of 1974³⁴ and operated for four years, until 1978.³⁵ Pursuant to the Commission's recommendations, the federal regulations underwent revision in 1981, and they have remained in effect since then.³⁶

III. THE FEDERAL REGULATIONS THAT GOVERN IRBS AND INFORMED CONSENT

A. *What Is Regulated?*

Research studies, generally termed "clinical trials," for the development of new drugs and devices are regulated by the FDA.³⁷ Medications that are the focus of study in clinical trials are called investigational new drugs (INDs).³⁸ Clinical trials that involve treatments

³¹ *Id.*; Vanderpool, *supra* note 2, at 9.

³² CURRAN ET AL., *supra* note 30, at 276.

³³ Vanderpool, *supra* note 2, at 10.

³⁴ See National Research Service Award Act of 1974, Pub. L. 93-348, 88 Stat. 342 § 201; McCarthy, *supra* note 29, at 58-59.

³⁵ BARUCH A. BRODY, *ETHICAL ISSUES IN DRUG TESTING, APPROVAL AND PRICING* 103 (1995).

³⁶ Vanderpool, *supra* note 2, at 10.

³⁷ 21 C.F.R. § 7.3(f) (2002) ("Product" means an article subject to the jurisdiction of the Food and Drug Administration, including any food, drug, and device intended for human or animal use....)

³⁸ 21 C.F.R. § 312.23(a) (2002). Medical research for drugs is conducted in three or four phases of clinical trials. See generally § 312.23. In Phase I, the new drug or treatment is given to patients or healthy individuals to determine its toxicity, most effective method of administration, and safe dosage range. *Id.* Participants in the trial receive increasing dosages of the substance in order to determine its metabolism, absorption, and side effects and to gain early evidence of its effectiveness, if possible. *Id.* Phase I clinical trials generally involve only 20 to 80 subjects, last about a year, and have a very high failure rate. Seventy percent of drugs submitted for Phase I clinical trials fail to progress to Phase II. See Veronica Henry, *Problems with Pharmaceutical Regulations In the United States*, 14 J. LEGAL MED. 617 (1993).

other than drugs and devices, such as surgery or bone marrow transplants, are not regulated by the FDA and are subject to DHHS regulation only if they are "conducted, supported or otherwise subject to regulation by any federal department or agency...."³⁹

B. IRBs

Research that is conducted, supported, or regulated by DHHS, the FDA, or another federal agency must be reviewed by an IRB.⁴⁰ An IRB is a committee designated by an institution to provide initial approval and periodic monitoring for biomedical research studies.⁴¹ The IRB's primary purpose is to protect the rights and welfare of human subjects.⁴² The IRB reviews a document known as the "protocol" for each proposed clinical trial, which describes the objectives of the research, its procedures, eligibility requirements for participants, the number of subjects to be tested, and other details.⁴³ The material submitted to the IRB also includes a document known as the "informed consent" form, which is given to all potential enrollees in order to provide them with a detailed explanation of the clinical trial and an opportunity to agree to participation in the study.⁴⁴

Phase II trials are designed to determine the effectiveness of the therapy. *Id.* The treatment is administered to patients suffering from the condition for which the therapy is intended. The trial often involves 100 to 300 people and lasts about two years. *Id.* Approximately 33% of drugs submitted for clinical trials fail in Phase II testing. *Id.*

Phase III clinical trials are conducted only after the treatment has proven effective through Phase I and II trials. *Id.* The third phase attempts to assess the medical results of the experimental therapy in comparison with standard therapy or no therapy at all. *Id.* Phase III studies usually involve several hundred to several thousand patients and last about three years. *Id.*

The FDA may also require post marketing or Phase IV clinical trials. *Id.* These studies are designed to determine the existence of less common adverse reactions, the effect of the drug on morbidity or mortality, or the effect of the drug on a particular patient population, such as children. *See* 21 C.F.R. §§ 312.21, 312.85 (2002); *See also* Veronica Henry, *Problems with Pharmaceutical Regulation in the United States*, 14 J. LEGAL MED. 617, 621-22 (1993).

³⁹ 45 C.F.R. § 46.101(a) (2001); *See also* Richard S. Saver, Note, *Reimbursing New Technologies: Why Are the Courts Judging Experimental Medicine?*, 44 STAN. L. REV. 1095, 1110-11 (1992); Norman Daniels & James E. Sabin, *Last Chance Therapies and Managed Care: Pluralism, Fair Procedures, and Legitimacy*, HASTINGS CENTER REPORT, Mar.-Apr. 1998, at 29.

⁴⁰ 21 C.F.R. §§ 56.101(a), 56.103 (2002); 45 C.F.R. § 46.101(a) (2001).

⁴¹ 21 C.F.R. § 56.102(g) (2002); 45 C.F.R. § 46.102(g) (2001).

⁴² 21 C.F.R. § 56.102(g) (2002).

⁴³ 21 C.F.R. § 56.115 (a) (2) (2002); 45 C.F.R. § 46.115 (a) (1) (2001).

⁴⁴ 21 C.F.R. § 50.20 (2002); 45 C.F.R. § 46.116 (2001).

After the IRB approves the informed consent form, all those who wish to become human subjects must sign a copy of the document, affirming the voluntariness of their choice.⁴⁵

The structure and duties of IRBs are governed by the DHHS and FDA regulations.⁴⁶ Each IRB must be composed of at least five members with diverse cultural and ethnic backgrounds, and both men and women should be included.⁴⁷ At least one member of the IRB should be a person whose principal concerns are in the scientific realm, and one individual's expertise should be nonscientific (e.g. a lawyer or minister).⁴⁸ Furthermore, to enhance its objectivity, each IRB must include at least one member who is not otherwise affiliated with the research facility and who has no immediate family members affiliated with the entity.⁴⁹ According to DHHS's Office for Protection from Research Risks (OPRR), now renamed the Office for Human Research Protection (OHRP), eighty-six percent of IRB members in 1995 were affiliated with academic research institutions as full-time faculty (56%), clinical and research staff (18%), and administrators (6%).⁵⁰ Academic institutions do not compensate IRB members for their work, and thus these individuals must volunteer their time without receiving payment or relief from other job duties.⁵¹

Unless an expedited review is conducted, research protocols must be reviewed at IRB meetings at which a majority of members are present, including a member whose expertise is nonscientific.⁵² Decisions concerning approval of each study are made by majority vote.⁵³

The IRB may approve, disapprove, or require modifications to the proposed research activities.⁵⁴ Investigators must be given written notification of the IRB's decisions, and IRBs are required to monitor the clinical trials they approve at intervals of at least once a year, or more

⁴⁵ 21 C.F.R. § 56.111(a)(4) (2002); 45 C.F.R. § 46.111(a)(4) (2001).

⁴⁶ 21 C.F.R. § 56.101 (a) (2002); 45 C.F.R. § 46.101 (a) (2001).

⁴⁷ 21 C.F.R. § 56.107(a) (2002); 45 C.F.R. § 46.107(a)-(b) (2001).

⁴⁸ 21 C.F.R. § 56.107(c) (2002); 45 C.F.R. § 46.107(c) (2001).

⁴⁹ 21 C.F.R. § 56.107(d) (2002); 45 C.F.R. § 46.107(d) (2001).

⁵⁰ JAMES BELL et al., EVALUATION OF NIH IMPLEMENTATION OF SECTION 491 OF THE PUBLIC HEALTH ACT, MANDATING A PROGRAM OF PROTECTION FOR RESEARCH SUBJECTS, FINAL REPORT 17 (1998).

⁵¹ Kerry Burke, *Loose-Fitting Genes: The Inadequacies in Federal Regulation of Institutional Review Boards*, 3 B.U. J. SCI. & TECH. L. 10, 38 (1997).

⁵² 21 C.F.R. § 56.108(c) (2002); 45 C.F.R. § 46.108(b) (2001).

⁵³ 21 C.F.R. § 56.108(c) (2002); 45 C.F.R. § 46.108(b) (2001).

⁵⁴ 21 C.F.R. § 56.109(a) (2002); 45 C.F.R. § 46.109(a) (2001).

frequently, depending on the severity of the risks entailed.⁵⁵ This periodic monitoring is known as "continuing review."⁵⁶

Before approving a clinical trial, the IRB must ensure that specific criteria are met. These include: (1) risks to participants are minimized; (2) risks to subjects are reasonable in light of anticipated benefits; and (3) selection of participants is equitable, and the protocol is sensitive to the particularized problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled individuals, or economically or educationally deprived persons.⁵⁷

C. *Informed Consent*

The contents of informed consent forms are also governed by the federal regulations. The informed consent document must be written in language that is accessible to subjects.⁵⁸ Informed consent may not include language that waives any of the subject's rights or releases the institution or research personnel from liability for negligence.⁵⁹ The regulations further require that informed consent be obtained in writing from each enrollee, though they allow for certain exceptions.⁶⁰

The regulations specify certain data that must be featured on the informed consent document. This information includes a description of the research, an explanation of risks, benefits, and alternatives, a discussion of confidentiality, a list of contact people, and a statement that participation is voluntary and may be discontinued at any time.⁶¹

⁵⁵ 21 C.F.R. § 56.109(e)-(f) (2002); 45 C.F.R. § 46.109(d)-(e) (2001).

⁵⁶ 21 C.F.R. § 56.109(f) (2002); 45 C.F.R. § 46.109(e) (2001).

⁵⁷ 21 C.F.R. § 56.111(a) (2002); 45 C.F.R. § 46.111(a) (2001).

⁵⁸ 21 C.F.R. § 50.20 (2002); 45 C.F.R. § 46.116 (2001).

⁵⁹ 21 C.F.R. § 50.20 (2002); 45 C.F.R. § 46.116 (2001).

⁶⁰ 21 C.F.R. § 50.27 (2002); 45 C.F.R. § 46.117 (2001).

⁶¹ 21 C.F.R. § 50.25(a) and (b) (2002); 45 C.F.R. § 46.116(a) and (b) (2001). The

provisions read as follows:

(a) Basic elements of informed consent. [I]n seeking informed consent the following information shall be provided to each subject:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject; A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (3) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (4) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(continued)

D. Research Involving Only Existing Medical Records Or Tissue Samples

In some cases investigators conduct research that does not involve treatment of any human subject. Instead, the research entails the study of existing medical records or tissue samples.⁶² For example, researchers might want to determine whether patients who have a particular type of cancer suffered certain symptoms before their diagnosis and might attempt to make that determination through an examination of their recorded medical histories. Investigators are not required to obtain informed consent from subjects for such research if the information is publicly available or if the researcher will record the data in a way that will make it impossible for subjects to be identified.⁶³

In addition, the regulations provide that an IRB may waive informed consent requirements if it finds “[t]hat the research presents no more than

(5) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained;

(6) An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject; and

(7) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new finding developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

45 C.F.R. § 46.116(a) and (b) (2001).

⁶² 45 C.F.R. § 46.101 (b)(4) (2001).

⁶³ *Id.*

minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context."⁶⁴ Accordingly, in limited circumstances in which subject welfare will not be compromised, this provision could allow for the use of identifiable medical records without subject consent.⁶⁵

IV. DEFICIENCIES IN THE REGULATORY SYSTEM

A. IRB Workloads

A 1998 statement issued by the Office of Inspector General of the U.S. Department of Health and Human Services (OIG) was highly critical of contemporary research oversight.⁶⁶ The OIG stated that the enormous workloads of many IRBs currently prevent them from adequately performing their review functions. A follow-up report issued by the Office of Inspector General in April of 2000 concluded that in the intervening two years, only minimal progress had been made to diminish the workload pressures of IRBs.⁶⁷ The number of initial reviews conducted by IRBs increased by an average of forty-two percent from 1993 to 1998, and some IRBs review up to 2,000 protocols per year.⁶⁸ Some IRBs also receive 200 or more reports of adverse events each month concerning the clinical trials they oversee.⁶⁹ An external review conducted at Johns Hopkins University after the death of a healthy human subject revealed that until June of 2001 a single IRB, meeting every two weeks, was responsible for the approval of 800 new protocols and the annual reviews they generated.⁷⁰ The reviewers emphatically stated: "[w]e view this as grossly

⁶⁴ 45 C.F.R. § 46.117(c)(2) (2001).

⁶⁵ 45 C.F.R. Pts. 160, 164; Jennifer Kulynych & David Korn, *The Effect of the New Federal Medical-Privacy Rule on Research*, 346 N. ENGL. J. MED. 201, 201-04 (2002) (discussing new privacy rule that became effective on Apr. 14, 2001. Most health care providers will be required to comply with the new rule by Apr. 2003); *See also Standards for Privacy of Individually Identifiable Health Information*, available at <http://www.hhs.gov/ocr/hipaa/finalmaster.html> (last visited July 9, 2001). The use and disclosure of protected health information is addressed in 45 C.F.R. §§ 164.501, 164.508(f), and 164.512(i).

⁶⁶ *See* 1998 Hearing, *supra* note 9.

⁶⁷ *Protecting Human Research Subjects: Status of Recommendations* (2000) (Office of Inspector General, Department of Health and Human Services), available at 2000 WL 553517, at *3.

⁶⁸ *Id.* at *5. The average local IRB meeting was found to last approximately 2.5 hours and to include 18 initial reviews, 9 expedited reviews, 43 amendments to protocols and 21 adverse-event reports. *Id.* at *6.

⁶⁹ *Id.*

⁷⁰ Steinbrook, *supra* note 12, at 719.

inadequate.”⁷¹ As noted above, most IRB members have full time jobs on the faculties or staffs of research institutions,⁷² and are not paid for their IRB services or relieved of other work duties.⁷³ Consequently, the time members can spend on IRB work is limited, and IRBs generally meet only once or twice a month for a few hours.⁷⁴

OPRR expressed concern that the IRBs’ work is also hampered by deficient expertise and resources.⁷⁵ Some IRB members lack in-depth understanding of the federal regulations governing biomedical research, and IRBs do not have the space, privacy, and level of staff support necessary to perform their duties adequately.⁷⁶ Small IRBs may have only one salaried staff member to coordinate all IRB activities and perform administrative tasks.⁷⁷

If IRBs become frequent defendants in lawsuits,⁷⁸ the IRB system may be fundamentally threatened. Since IRBs rely heavily on the work of volunteers, they may find it difficult to recruit members in the future. Physicians who are concerned about potential liability may be very reluctant to offer their services to IRBs.⁷⁹

B. *Flaws In The Informed Consent Process*

An increasing volume of evidence indicates that the informed consent process is severely flawed in many cases. Often, human subjects either are given insufficient information or do not comprehend the data they receive.

The 1998 OIG statement was very critical of informed consent procedures.⁸⁰ It noted, for example, that a 1995 Advisory Commission on

⁷¹ Steinbrook, *supra* note 12, at 719.

⁷² See BELL, *supra* note 50 and accompanying text.

⁷³ Steinbrook, *supra* note 12, at 717; Burke, *supra* note 51, at 38.

⁷⁴ Steinbrook, *supra* note 12, at 719.

⁷⁵ U.S. DEP’T OF HEALTH & HUMAN SERVS., OFFICE FOR HUMAN RESEARCH PROTS., OHRP COMPLIANCE ACTIVITIES: COMMON FINDINGS AND GUIDANCE (Sept. 1, 2000), available at <http://ohrp.osophs.dhhs.gov/references/findings.pdf>. [hereinafter OHRP].

⁷⁶ *Id.*

⁷⁷ 1998 Hearing, *supra* note 9.

⁷⁸ See e.g., Robertson v. McGee, No. 4:01-CV- 60 (N.D. Okla.) (filed Jan. 29, 2001).

⁷⁹ Alan Milstein, an attorney who has filed several lawsuits against physician investigators on behalf of clinical trial participants, has publicly criticized IRBs as sharing the blame for alleged injuries to human subjects. In one article he stated that “[I]n our major institutions, where you’ve got Nobel scientists and Nobel doctors and well-regarded professors, the IRBs more or less simply rubber-stamp whatever protocol one of these men put before them.” Foubister, *supra* note 14, at 1.

⁸⁰ See 1998 Hearing, *supra* note 9.

Human Radiation Experiments found, after interviewing actual subjects that few realized they were involved in research, and many had little understanding of the informed consent forms they had signed.⁸¹

Commonly, the problem is confusion about the differences between research and clinical treatment.⁸² While some research subjects are healthy volunteers who would not otherwise seek medical treatment, many are patients with particular illnesses who are recruited for clinical research by their treating physicians. These patients are vulnerable to a phenomenon known as the "therapeutic misconception."⁸³ Because they are sick and are recruited for enrollment by their doctors, they become convinced that their research participation will be of definite medical benefit to them. These patients are therefore resistant to explanations that treatments involved in clinical trials are unproven and experimental, no matter how clearly and explicitly these explanations are given.

Numerous studies have focused on the issue of informed consent and have revealed very troubling evidence concerning the ability of research subjects to provide valid consent.⁸⁴ In a labor-induction study with fifty-two participants, thirty-nine percent of the women were found to be unaware that they were participating in a research study although all had

⁸¹ See 1998 Hearing, *supra* note 9.

⁸² CHARLES LIDZ ET AL., INFORMED CONSENT: A STUDY OF DECISIONMAKING IN PSYCHIATRY 28 (1984); See also Paul S. Appelbaum et al., *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17 HASTINGS CENTER REP. 20 (1987). The authors explain the problem as follows:

Most people have been socialized to believe that physicians (at least ethical ones) always provide personal care. It may therefore be very difficult, perhaps nearly impossible, to persuade subjects that *this* encounter is different, particularly if the researcher is also the treating physician, who has previously satisfied the subject's expectations of personal care. Further, insofar as much clinical research involves persons who are acutely ill and in some distress, the well-known tendency of patients to regress and entrust their well-being to an authority figure would undercut any effort to dispel the therapeutic misconception.

Id.

⁸³ Evan G. DeRenzo et al., *Assessment of Capacity to Give Consent to Research Participation: State-of-the-Art and Beyond*, 1 J. HEALTH CARE L. & POL'Y 66, 72 (1998); See also Holly A. Taylor, *Barriers to Informed Consent*, 15 SEMINARS IN ONCOL. NURS. 89, 91 (1999) (noting that oncology patients often perceive enrollment in a research protocol as their last chance to receive effective treatment).

⁸⁴ DeRenzo, *supra* note 83, at 69; Janet Fleetwood, *Conflicts of Interest in Clinical Research: Advocating for Patient-Subjects*, 8 WIDENER L. SYMP. J 105, 108 (2001).

signed informed consent forms.⁸⁵ Even those who realized they were research subjects often misunderstood essential aspects of the study and their role in it.⁸⁶

Several investigators asked fifty cancer patients to review a hypothetical consent form for participation in a placebo-controlled clinical trial.⁸⁷ Subjects were asked to interpret four different statements in the consent form.⁸⁸ Depending on the statement, the subjects provided incorrect answers twenty-six to fifty-four percent of the time.⁸⁹

In another survey, forty-seven percent of responding researchers indicated that they thought few of their subjects, enrolled in multinational studies in the 1980s, knew they were participating in controlled experiments, even though they had given written consent.⁹⁰ In two additional studies, over three quarters of physicians who were questioned believed that subjects rarely understood all the data given to them.⁹¹

The difficulty of obtaining informed consent is exacerbated by the fact that informed consent documents are generally written in language that is technical and sophisticated and consequently inappropriate for the intended audience.⁹² While many informed consent documents require a college

⁸⁵ Bradford H. Gray, *Complexities of Informed Consent*, 437 ANNALS AM. ACAD. POL. & SOC. SCI. 37, 43 (1978). Gray states that the women's misunderstanding is attributable to several factors "including the generally low educational levels of the unaware subjects, the investigator's delegation to subordinates of the task of obtaining consent, seeking consent in the labor room, and providing little oral explanation - sign this and we can get started." *Id.*

⁸⁶ BRADFORD H. GRAY, HUMAN SUBJECTS IN MEDICAL EXPERIMENTATION 103 (1975); *See also* Angela Estey et al., *Are Research Subjects Able to Retain the Information They Are Given During the Consent Process?*, 3 HEALTH L. REV. 37 (1994). A study of 29 subjects from two clinical trials at the University of Alberta Hospitals revealed that 14 of them were unable to describe accurately the type of research study in which they were enrolled and 17 could not list any risks associated with participation in the trial although risks had been explicitly explained to them. *Id.* at 40.

⁸⁷ H. J. Sutherland et al., *Are We Getting Informed Consent for Patients with Cancer?*, 83 J. R. SOC. MED. 439 (1990).

⁸⁸ *Id.* at 440.

⁸⁹ *Id.* at 441.

⁹⁰ Sarah J.L. Edwards et al., *The Ethics of Randomized Controlled Trials from the Perspectives of Patients, the Public, and Healthcare Professionals*, 317 BRIT. MED. J. 1209, 1209 (1998).

⁹¹ *Id.* at 1209-10.

⁹² Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 36 (1993); *See also* Christopher Daugherty et al., *Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials*, 13 J. CLIN. ONCOL. 1062, 1065 (1995); Daugherty found that the cancer patients' educational levels significantly influenced their ability to

level reading comprehension ability,⁹³ the average American has only an eighth grade reading comprehension level.⁹⁴ Rather than providing useful explanations for patients, the forms often serve to educate only the medically trained IRB members who review them.⁹⁵

The challenge of obtaining genuine consent from subjects has had grave consequences for some institutions. During 1998 and 1999, OPRR suspended federal research funding at Chicago's Rush-Presbyterian-St. Luke's Medical Center, the West Los Angeles VA Medical Center, Duke University Medical Center, the University of Illinois at Chicago, and six University of Colorado institutions, all of which are well-regarded research facilities.⁹⁶ In January of 2000, research activities were suspended at the University of Pennsylvania and the University of Alabama at Birmingham.⁹⁷ Prominent among the violations for which these entities

recall correctly the purpose of the phase I trials for which they were eligible to enroll. While 71% of college educated patients were able to state the purpose of phase I trials, only 20% of those without a college degree could do so. Similarly, Casselith discovered that patients with less than a high school education had difficulty remembering information about a research protocol in which they had just consented to participate. *Id.* Barrie R. Cassileth et al., *Informed Consent – Why Are Its Goals Imperfectly Realized?*, 301 N. ENGL. J. MED. 896, 898 (1980).

⁹³ Holly Taylor, *supra* note 83, at 93 (noting that “the average consent form is written at a level that requires at least a high school education or higher”); Henry W. Riecken & Ruth Ravich, *Informed Consent to Biomedical Research in Veterans Administration Hospitals*, 248 JAMA 344, 346 (1982) (noting that “most of the consent forms are written in language that requires reading ability at the college level for comprehension of the investigator’s purpose,” and that only 27% of VA patients surveyed “had more than a high school education.”).

⁹⁴ Terry C. Davis et al., *Reading Ability of Parents Compared with Reading Level of Pediatric Patient Education Materials*, 93 PEDIATRICS 460, 461-62 (1994); Stuart A. Grossman et al., *Are Informed Consent Forms That Describe Clinical Oncology Research Protocols Readable By Most Patients and Their Families?*, 12 J. CLIN. ONCOL. 2211, 2212 (1994).

⁹⁵ See Davis, *supra* note 94; Grossman, *supra* note 94.

⁹⁶ Vida Foubister, *More Centers Cited for Ethics Lapses in Research*, AM. MED. NEWS, Nov. 1, 1999, at 8, 10; See also AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, PROFESSIONAL ETHICS, Summer 1999, at 3 (noting that OPRR shut down 1,000 human research studies at the University of Illinois at Chicago and investigated the University of South Florida’s IRB).

⁹⁷ Marlene Cimons, *FDA cites violations, halts human gene therapy work at Penn*, THE PLAIN DEALER, Jan. 22, 2000, at 12A; Jay Reeves, *Order suspends university’s medical research*, THE PLAIN DEALER, Jan. 22, 2000, at 12A (reporting that the government suspended about 25% of research studies conducted at the University of Alabama at Birmingham).

were cited was the failure to obtain adequate informed consent from subjects.⁹⁸

B. Informed Consent Is Particularly Difficult To Obtain From Gravely Ill Patients

Genuine informed consent is particularly difficult to obtain when the patients at issue suffer from life-threatening diseases.⁹⁹ The decision-making capacity of gravely ill patients is often compromised by the emotional trauma of their illnesses or by various social and familial pressures. Consequently, those who have the most to gain or lose from receiving experimental treatment are also those who are least able to provide meaningful informed consent.

Illness can be viewed as an "ontological assault" that undermines the patient's identity by "attacking the fundamental unity of mind and body."¹⁰⁰ A patient suffering from multiple sclerosis described the experience of disease in these words:

The most deeply held assumption of daily life is the assumption that I, personally, will continue to be alive and it is in light of this assumption that one engages in daily activities. The onset of illness, however, brings one concretely face-to-face with personal vulnerability.... Thus, the person who is ill ... is unable readily to fit illness into the typified schema used to organize and interpret experience.... One finds oneself preoccupied with the demands of the here and now, confined to the present moment, unable effectively to project into the future.¹⁰¹

Commentators have noted that serious sickness creates in patients a strong desire to be cared for and to be free of the responsibility and stress of decision-making, as though they were once again children.¹⁰² Many scholars have noted that the thought processes of those suffering from prolonged or serious illnesses are often impaired and have urged that research protocols involving such patients be subject to heightened IRB scrutiny.¹⁰³ One informed consent study found that as the seriousness of the

⁹⁸ Foubister, *supra* note 96, at 8, 10; Cimon, *supra* note 97, at 12-A; See also OHRP, *supra* note 75.

⁹⁹ Fleetwood, *supra* note 84, at 107.

¹⁰⁰ MARK A. HALL, MAKING MEDICAL SPENDING DECISIONS 36 (1997).

¹⁰¹ *Id.* at 28.

¹⁰² *Id.*

¹⁰³ Alison Wichman, *Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval*, 1 J. HEALTH CARE L. & POL'Y 88, 93 (1998) ("People suffering from prolonged or serious illnesses that are refractory to standard

(continued)

illness increases, the ability of potential subjects to remember information relevant to their research participation decreases.¹⁰⁴ Seriously ill patients may experience depression, extreme anxiety, rage, denial, or desperation to find a cure, all of which may cloud their judgment and hamper their ability to evaluate the benefits and risks of a clinical trial.¹⁰⁵

therapies, or for which there are no standard therapies, should be considered vulnerable particularly when they are willing to take any risk for even a remote possibility of relief.”); DeRenzo et al., *supra* note 83, at 69, 78 (“[T]he majority of studies conclude that seriously ill research subjects have difficulties in many facets of providing ethically valid consent,” and “Serious disease produces desperation....[b]oth on the part of subjects and their families [that] can make persons vulnerable to manipulation”); George J. Annas, *The Changing Landscape of Human Experimentation: Nuremberg, Helsinki, and Beyond*, 2 HEALTH MATRIX 119, 134 (1992) (“Terminally ill AIDS and cancer patients can be harmed, misused, and exploited”); D. Christian Addicott, *Regulating Research on the Terminally Ill: A Proposal for Heightened Safeguards*, 15 J. CONTEMP. HEALTH L. & POL’Y 479, 493 (1999) (“[T]he terminally ill share a number of relevant characteristics with the vulnerable populations listed in the regulations, [and thus] an IRB would be well within its authority to treat the terminally ill as vulnerable”); Sarah Hewlett, *Consent to Clinical Research – Adequately Voluntary or Substantially Influenced?*, 22 J. MED. ETHICS 232, 233 (1996) (noting that patients dealing with illness may experience a reduction in their autonomy due to a variety of factors related to the physiologic and psychological impact of illness).

¹⁰⁴ Monica H. Schaeffer et al., *The Impact of Disease Severity on the Informed Consent Process in Clinical Research*, 100 AM. J. MED. 261, 264 (1996). The study involved 127 subjects who were recruited from four different research protocols at the National Institute of Health. *Id.* Nine subjects had metastatic cancer for which all treatment had thus far failed and were offered a Phase I study. *Id.* Thirty-six subjects had recurrent ovarian cancer and were offered a Phase II trial. *Id.* Twenty eight subjects were infected with the HIV virus and were offered participation in a Phase III clinical trial. *Id.* Finally, 54 subjects were healthy volunteers who were enrolled in positron emission tomography studies. *See id.* at 261-62.

While the ability of patients to remember information associated with their clinical trials generally decreased as the severity of their illness increased, there were several exceptions to this finding. *Id.* at 264. Immediate retention of information regarding clinical trial procedures increased as the severity of illness increased. *Id.* In addition, Phase I and II subjects showed the best long-term retention, while Phase III participants and healthy volunteers retained the least on a long-term basis. *Id.* Finally, retention of information about alternative therapies was the same among the three groups of sick subjects. *Id.*

See also Cassileth, *supra* note 92, at 898 (noting that “[b]edridden patients gave significantly fewer correct responses to each item on the recall test [concerning chemotherapy, radiation therapy, or surgery, to which they had consented the previous day] than did ambulatory patients”).

¹⁰⁵ Addicott, *supra* note 103, at 502-03; Hewlett, *supra* note 103, at 233.

V. RECOMMENDATIONS

A. IRBs

It is clear that many IRBs inadequately perform their oversight functions. Their deficient performance, however, does not stem from deliberate misconduct or indifference towards the welfare of human subjects, but rather, from inadequate resources, unmanageable workloads, and, in some cases, insufficient expertise.¹⁰⁶ Alleviating these problems is essential to enhancing protection for clinical trial participants.

An effective means of improving the functioning of IRBs would be the addition of more full-time, paid, professionals to their staffs. The size of the professional staff would vary in accordance with the workloads of the IRBs. The professional staff members should be charged with the review of all protocols that are submitted for initial approval, amendment, and continuing review to the IRB. One or two members of the IRB with relevant medical expertise should also read each protocol and provide comments to the staff.¹⁰⁷ The professional staff should then provide written reports to the full IRB membership, summarizing the protocol and their recommendations. The IRB volunteers would be responsible for reading the reports, asking follow-up questions, and voting on whether to approve the protocol.

Under this system, each IRB member will not be required to read every page of every protocol, many of which are quite voluminous, and therefore IRB duties will become less burdensome. The system will also expedite the review process so that investigators will not have to wait several months for approval of their submitted proposals. Finally, professional staffs would assure that each protocol actually receives a thorough and systematic initial review and continued monitoring, which many commentators have suggested does not always occur when these tasks are left exclusively in the hands of well-meaning, but overworked volunteers.¹⁰⁸

Additional funding would obviously be needed to support the hiring of adequate professional staffs. To obtain the necessary economic support, IRBs could charge commercial research sponsors for review of their protocols. Similarly, if the research is sponsored by a governmental entity, the sponsor could be required to add a fixed sum or a small percentage to

¹⁰⁶ See Malinowski, *supra* note 7, at 63; Fleetwood, *supra* note 84, at 111.

¹⁰⁷ Thus, a protocol relating to cancer treatment would be reviewed by professional staff members and by one or more oncologists, and a protocol relating to therapy for heart disease would be reviewed by one or more cardiologists in addition to the professional staff.

¹⁰⁸ See discussion *supra* Part III.A.

its grant in order to support IRB activities.¹⁰⁹ Nothing in the federal regulations prohibits the imposition of such charges.

B. *Informed Consent Procedures*

Professor Jay Katz of Yale Law School has warned that obtaining true informed consent is an "inordinately difficult task."¹¹⁰ He suggests that researchers must disclose to study participants at least the following data:

(1) that the subjects are not only patients and, to the extent to which they are patients, that their therapeutic interests, even if not incidental, will be subordinated to scientific interests; (2) that it is problematic and indeterminate whether their welfare will be better served by placing their medical fate in the hands of a physician rather than an investigator; (3) that in opting for the care of a physician they may be better or worse off and for such and such reasons; (4) that clinical research will allow doctors to penetrate the mysteries of medicine's uncertainties about which treatments are best, dangerous, or ineffective; (5) that clinical research may possibly be in the patient's immediate best interest, perhaps promise benefits in the future, or provide no benefit, particularly if the patient is assigned to a control (placebo) arm of a study; (6) that research is governed by a research protocol and a research question and, therefore, his or her interests and needs will yield to the claims of science; and (7) that physician-investigators will respect whatever decision the subject ultimately makes.¹¹¹

To these I would add a few other suggestions. Much of the general information discussed by Professor Katz should be included in a video shown at the beginning of the informed consent process. The video should clearly explain the difference between research and therapy and describe to subjects their obligation to provide meaningful consent. In this television age, people often find audio-visual aids to be an accessible and effective communication tool that is an essential supplement to written materials and verbal presentations. Educational videos have been successfully used by many doctors. In 1998, for example, the Foundation for Informed Medical Decision Making produced a video entitled "The PSA Decision: What

¹⁰⁹ For a detailed discussion of recommendations for the enhancement of IRB effectiveness see Sharona Hoffman, *Continued Concern: Human Subject Protection, the Institutional Review Board, and Continuing Review*, 68 TENN. L. REV. 725 (2001).

¹¹⁰ Katz, *supra* note 92, at 34.

¹¹¹ *Id.*

You Need to Know," which was intended to assist asymptomatic men over 50 in deciding whether to undergo prostate-specific antigen (PSA) tests.¹¹²

The informed consent process should also include a thorough discussion between the potential subject and the investigator or a research nurse, in which all the details of the trial are verbally explained.¹¹³ Potential participants should then be quizzed to ascertain that they fully understand the information they have received and to determine whether they are able to articulate answers to specific questions.¹¹⁴ The informed consent process should continue until the investigator is satisfied that the potential subject understands all necessary information.¹¹⁵ Those who fail to demonstrate a satisfactory level of comprehension after the investigator or a nurse has invested a reasonable amount of time and effort in the informed consent process should not be enrolled as human subjects.¹¹⁶

To facilitate reading comprehension, informed consent documents should be written in simple language that can be understood by people with an eighth grade reading level.¹¹⁷ If at all possible, IRBs should include at least one member with expertise in reading comprehension or elementary education who could scrutinize informed consent forms to determine their readability and recommend simplifications where appropriate.¹¹⁸

¹¹² THE PSA DECISION: WHAT YOU NEED TO KNOW, (The Foundation for Informed Medical Decision Making (1998)).

¹¹³ See Riecken & Ravich, *supra* note 93. The article discusses a survey of 188 male veteran patients who were human subjects in research projects in four VA hospitals. Thirty seven principal investigators were also surveyed. Of investigators who were personally responsible for explaining the study to patients, approximately half reported that they spent less than 15 minutes obtaining informed consent from patients, and a third stated that they spent between 15 and 30 minutes. Riecken & Ravich, *supra* note 93, at 345. Twenty-eight percent of research participants did not realize that they were enrolled in a clinical trial, and they were concentrated in the studies in which the investigators invested the shortest periods of time in the consent process. Riecken & Ravich, *supra* note 93, at 345. Only one investigator had no unaware participants. He had given each potential subject a short examination after providing an explanation of the study. If the patient did not pass, the trial was described again. Riecken & Ravich, *supra* note 93, at 347.

¹¹⁴ See Katz, *supra* note 92, at 36-37.

¹¹⁵ See Katz, *supra* note 92, at 36.

¹¹⁶ See Riecken & Ravich, *supra* note at 93.

¹¹⁷ Grossman., *supra* note 94, at 2212. The authors found that the typical consent form that describes a clinical oncology protocol is "too complex to be read by most patients and their families." The average person reads at approximately an eighth grade reading level, and the mean grade level required for comprehension of the forms that were studied was between 11.1 and 14.1, depending on the index used. See *id.*

¹¹⁸ 21 C.F.R. §56.108(c); 45 C.F.R. § 46.108(b). IRBs must include at least one community representative whose primary concerns are nonscientific. 21 C.F.R. §56.108(c);
(continued)

C. *Storage Of Blood And Tissue Samples For Future Genetic Testing*

Many clinical trials include blood tests or tissue biopsies. Once testing has been completed for purposes of the study, investigators often wish to store the blood or tissue samples for purposes of future genetic testing.¹¹⁹ It is difficult to obtain meaningful informed consent for unknown future studies because researchers cannot accurately describe the research that will be conducted or the data that will be sought.

In addition, genetic testing raises important concerns about privacy and potential discrimination.¹²⁰ If confidentiality is not properly maintained and genetic data about an individual is disclosed to third parties, such as employers and insurers, the individual might suffer discrimination.¹²¹ For example, genetic testing might reveal that a person is susceptible to a particular cancer, leading employers who obtain these test results to decline to hire her and insurers to deny her coverage because of anticipated costs that will be generated by her likely poor health status in the future.¹²²

Consequently, it is important that careful efforts be made to obtain informed consent for the storage of blood and tissue samples for purposes of future genetic testing.¹²³ Consent for tissue storage should be separate from consent for the underlying clinical trial, and thus, the subject should receive two consent documents and be required to provide two consent signatures for studies that contemplate future genetic testing. Subjects must be alerted to the fact that the issue of tissue storage is different from the issue of participation in the underlying trial and that it requires a separate decision-making process.

The consent form should address how confidentiality will be safeguarded and inform subjects about whether their samples will be de-identified. It should also disclose to participants that they will not personally benefit from future genetic testing in that researchers will not

45 C.F.R. § 46.108(b). The regulations do not specify what the community representative's nonscientific expertise should be. *See id.* In light of contemporary concerns about the readability of informed consent documents, however, IRBs would be wise to choose a layperson whose field of specialty is reading comprehension or elementary education.

¹¹⁹ George J. Annas, *The Limits of State Laws to Protect Genetic Information*, 345 N. ENGL. J. MED. 385, 387 (2001).

¹²⁰ *Id.*

¹²¹ *Id.*; *See also* Mark A. Rothstein & Sharon Hoffman, *Genetic Testing, Genetic Medicine, and Managed Care*, 34 WAKE FOREST L. REV. 849, 865-71.

¹²² Annas, *supra* note 120.

¹²³ One commentator states that in reality what is being obtained is a waiver of informed consent, because the subject generally agrees not to be notified about or consent to future testing. Interview with Pilar Ossorio, Assistant Professor of Law, University of Wisconsin Law School (Nov. 30, 2001).

contact subjects or their doctors to provide test results. Furthermore, subjects should be informed that the research sponsor might profit from future research if it develops a new drug or therapy that is successfully marketed but that the individuals whose samples were utilized will not receive a share of the sponsor's earnings.

Finally, the consent form should provide subjects with choices as to the type of research to be conducted using their samples. For example, participants in a clinical trial relating to breast cancer who agree to storage of their samples could be asked to select from among the following: 1) I agree to have my sample used for future genetic testing related to breast cancer; 2) I agree to have my sample used for future genetic testing related to diseases other than breast cancer; and 3) I agree to have my sample stored but wish the investigator to contact me for permission before any testing is conducted in the future. If subjects read, think about, and respond to specific questions, investigators can be reassured that participants have understood the choices they were required to make and have provided meaningful consent.

VI. CONCLUSION

Enhancement of protections for human subjects will undoubtedly impose added costs for clinical research. Increasing the number of IRB professionals will require funding by private and governmental research sponsors.¹²⁴ A conscientious effort to obtain meaningful consent may delay recruitment of subjects and completion of research.¹²⁵ A valid informed consent process may require several hours or even repeated conversations over a few days.¹²⁶ Furthermore, if patients fully understand all components and risks of a protocol, they may more often refuse to enroll, making some studies difficult or, in rare cases, impossible to conduct.¹²⁷ These negative consequences, however, are outweighed by the advantages of enhancing the integrity of biomedical research, bolstering human subject protection, and reducing the likelihood of liability associated with clinical studies.

¹²⁴ See Katz, *supra* note 92, at 38.

¹²⁵ Katz, *supra* note 92, at 36.

¹²⁶ Riecken & Ravich, *supra* note 93, at 345-47.

¹²⁷ See Gina Kolato & Kurt Eichenwald, *Hope for Sale: A Special Report; Business Thrives on Unproven Care, Leaving Science Behind*, N.Y. TIMES, Oct. 3, 1999, at A1 (discussing the difficulties faced by some investigators who wish to recruit patients to participate in clinical trials involving treatments for serious illnesses such as cancer, heart failure, and Parkinson's disease). *Id.*